## *REMARKS*

Claims 1-50 are pending in the application. Claims 12, 13, 15, 17 and 24-50 have been withdrawn from consideration. Claims 9, 10, 16, and 23 have been canceled. Claims 1, 2, and 11 have been amended. Applicants submit that amendments to claims 1 and 2 are supported in the instant specification. Specifically, support for the amendments can be found at page 3, lines 24-26; page 5, lines 3-6; page 8, line 28 through page 9, line 7; and page 13, lines 27-29 of the specification as-filed. The amendment to claim 11 is clerical in nature. Thus, no new matter has been added.

## *CLAIM REJECTIONS*

### *35 U.S.C. § 112, 2nd Paragraph Rejections*

The Examiner has rejected claims 1-11, 14, 16 and 18-23 for failing to particularly point out and distinctly claim the subject matter. Claim 1 has now been amended to recite: "A method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time, inhibiting differentiation of the stem and/or progenitor cells...", thereby overcoming the Examiner's rejection thereof on the basis of 35 U.S.C. § 112, second paragraph.

### *35 U.S.C. § 112, First Paragraph Rejections*

The Examiner has rejected claims 1-11, 14, 16 and 18-23, under 35 USC § 112 first paragraph, as lacking enablement in the specification commensurate with the scope of the claimed inventions. The Examiner's rejections are respectfully traversed. Claims 9-10, 16 and 23 have now been cancelled, rendering moot the rejection thereof. Claims 1, 2 and 11 have now been amended.

The Examiner, while acknowledging that the instant specification is enabling for a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising culturing CD34+ and/or CD133+ enriched undifferentiated hematopoietic stem and/or progenitor cells derived from bone marrow, mobilized peripheral blood or umbilical cord blood, in a bioreactor under conditions comprising the cytokines TPO, IL-6, SCF, FLT-3 ligand and 2-15 μM of the copper chelator TEPA, has alleged that the specification lacks enablement for the method comprising culturing any population of cells comprising stem and/or progenitor cells in a bioreactor under conditions comprising any copper chelator, in an undefined medium. Applicant disagrees.

The Examiner has alleged that the specification is silent regarding culture, expansion and prevention of differentiation of hematopoietic stem and/or progenitor cells that did not

undergo pre-selection and enrichment for CD34+ or CD133+ stem cell markers. Applicants wish to point out that, contrary to the Examiner's assertions, Example 2 of the instant specification clearly shows enhanced expansion of hematopoietic stem and/or progenitor cells (HSC) (as well as endothelial and mesenchymal stem cells) from unselected, total nucleated cells from the leukocyte-rich fraction of blood using the methods of the claimed invention (see, for example Brief Description of Drawings, pages 16-19, and FIGs. 3 and 6-8), as evidenced by fold expansion of the total cellular, CD34+ and CD133+ fractions. Thus, Applicant respectfully requests withdrawal of the rejection on the basis of culturing hematopoietic cells not undergoing pre-selection and enrichment for CD34+ or CD133+ stem cell markers.

Claims 1 and claims dependent therefrom are now drawn on methods for *ex-vivo* expansion of hematopoietic stem and/or progenitor cells by culturing in spinner flask or moving wall bioreactors with early acting cytokines and tetraethylenepentamine.

The Examiner has stated that the mechanisms that control proliferation, expansion and differentiation of stem cells are not yet completely understood, therefore rendering unpredictable the art of growing undifferentiated stem cells in culture, based on references Peters et al., Percival et al., and Lovejoy. Applicant disagrees.

Regarding Peters et al., Applicants wish to point out that Peters et al. reported on experiments using fetal liver (FL) putative hematopoietic cells. The cited passage relates to expansion of total FL cell numbers (see Peters et al., Fig. 1) over 60 days of culture, and does not provide any assessment of the stage of differentiation of the expanded. Further determinations of CD34+ expansion were conducted in "C1" expanded cultures, without comparison of culture conditions. Thus, contrary to the Examiner's assertions, the determination that a specific culture condition was more effective than others in expanding total FL cells in Peters et al. is irrelevant to the issue of determining culture conditions for expanding and at the same time inhibiting differentiation of stem and/or progenitor cells.

Regarding Percival et al., Applicant wishes to point out that Percival et al. studied the effects of copper on retinoic acid-stimulated differentiation (superoxide anion production) of a single in-vitro cell line, HL-60, which lacks the capability for spontaneous differentiation. Thus, Percival et al. did not study *ex-vivo* expansion and differentiation of hematopoietic cells as taught in the instant specification, but rather *in-vitro* growth of a cultured cell line:

> "As used herein the term "*ex-vivo*" refers to a process in which cells are removed from a living organism and are propagated outside the organism (e.g., in a test tube). As used herein, the term "*ex-vivo*", however, does not refer to a process by which cells known to

> propagate only *in-vitro*, such as various cell lines (e.g., HL-60, MEL, HeLa, etc.) are cultured."(page 36, lines 27-31 of the instant specification)

Further, Percival et al. pose the following question: "If copper is removed from the cell is differentiation impaired or prevented?" (see, Percival et al., page 1066S, column 2, lines 7-8). Thus, the HL-60 cells were exposed to both differentiation stimulus (retinoic acid) and a copper chelator (TEPA). Percival et al. report that TEPA had no effect on HL-60 differentiation: "Cells incubated with TEPA and retinoic acid produced the same amount of superoxide anion as did the cells with retinoic acid, indicating that differentiation had occurred." (see, Percival et al., page 1066S, column 2, lines 15-18), and conclude that "whereas our TEPA model is useful in some studies related to manipulating copper concentrations and Cu/Zn SOD activity, it does not prevent HL-60 cells from differentiating.", further stating that "The lack of effect of TEPA on HL-60 differentiation prompted us to develop a mouse model to continue our investigation of copper's role in granulopoiesis." (see, Percival et al., page 1066S, column 2, lines 31-33). No comparison of copper chelators is suggested or implied. Thus, contrary to the Examiner's assertions, Percival et al. do not report on the exact role of genus of copper chelators in expansion of HSC, or on the effectiveness of copper chelation with TEPA, but hypothesize on the role of copper in granulopoiesis, for which they determine that the TEPA model is not useful.

Regarding the effects of chelators such as EDTA and citrate, Applicant wishes to point out that the instant claims include the limitation of "...culturing said stem and/or progenitor cells *ex-vivo* in said bioreactor under conditions allowing for cell proliferation...". "Conditions for cell proliferation" are easily assessed by one of ordinary skill in the art (see, for example, Examples 1 and 2, Experimental Procedures, the instant specification, and US Patent No. 7,169,605 to Peled et al., incorporated by reference), thus chelators incompatible with cellular proliferation are easily identified and can be avoided without undue experimentation.

Regarding conditions allowing cell proliferation, Applicant wishes to point out that instant invention as claimed is the expansion, in a bioreactor, of hematopoietic cells from selected or unselected cells by provision of a transition metal chelator in the medium, in the presence of nutrients and cytokines, suitable for the proliferation of hematopoietic cells. It will be appreciated that the feature of the presence of specific combinations and concentrations of cytokines and nutrients, as for example disclosed in Examples 1 and 2, is but one embodiment of the actual invention:

> "Providing the *ex-vivo* grown cells with conditions for *ex-vivo* cell proliferation include providing the cells with nutrients and preferably with one or more cytokines, as is further detailed hereinunder"(page 37, lines 1-3 of the instant specification)

Thus, the specification enables a variety of conditions suitable for proliferation of hematopoietic stem cells from a number of sources.

Applicants respectfully submit that the Examiner's statement that the present invention must be considered unpredictable since the mechanisms controlling proliferation, expansion and differentiation of stem cells are as yet unknown is an improper basis by which to evaluate the enablement of the claimed invention. The Federal Circuit has stated in In re Cortright, 165 F.3d 1353 (1999):

> "It is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); see also Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). Furthermore, statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained."

Thus while a detailed understanding of the mechanisms of expansion proliferation, expansion and differentiation of stem cells will undoubtedly be of great value, such understanding is not necessary for enabling the claimed invention.

The abovementioned notwithstanding, and in order to expedite prosecution in this case, Applicants have chosen to amend claim 1 to include the limitations of culturing cell populations comprising stem and/or progenitor cells in the presence of early acting cytokines and tetraethylenepentamine, and in the absence of a stromal feeder layer. Such culture conditions have been shown effective in expanding yet inhibiting differentiation of stem and/or progenitor cells: For example, in PCT IL/99/00044, which is incorporated into the instant specification by reference, Peled et al. demonstrated *ex-vivo* expansion and inhibition of differentiation in hematopoietic stem and progenitor cells by culturing with copper chelators in the presence of a single early acting cytokine (see IL/99/00444, Fig. 20), and also in the presence of a variety of combinations of early acting cytokines (see IL/99/00444, Figs. 12-14). Support for such an amendment is found throughout the instant specification, for example, original claims 9-11 and Examples 1 and 2, and original claim 23.

In view of the arguments and amendments brought herein, Applicant believes to have overcome the 35 U.S.C. 112, first paragraph objections, and as such, respectfully requests the withdrawal thereof.

***35 U.S.C. § 102(b) Rejections: Peled et al (WO 99/40783)***

The Examiner has rejected claims 1-11, 14, 18 and 23 under 35 U.S.C. § 102(b), as allegedly being anticipated by Peled et al (WO 99/40783). Claims 9, 10, 16 and 23 have now been canceled, rendering moot the Examiner's rejection thereof. Claims 1, 2 and 11 have now been amended. The Examiner's rejections are respectfully traversed.

As detailed herein, the claimed invention is drawn on methods for the *ex-vivo* expansion of hematopoietic stem and/or progenitor cells by culturing, in a spinner flask or rotating wall vessel bioreactor under stromal- and feeder layer-free conditions allowing proliferation yet inhibiting differentiation of the stem and/or progenitor cells, wherein the conditions include the presence of early acting cytokines and copper chelators, as recited in amended claim 1.

Peled et al. (WO 99/40783) is silent regarding the culturing of cells in a spinner flask or rotating wall bioreactor (the terms do not appear in the entire document), but rather teaches the expansion of hematopoietic stem and/progenitor cells in static culture conditions in cell culture bags. Thus, Peled et al fails to teach all the elements of the instant specification, and such, does not and cannot anticipate the invention as claimed in now amended claim 1, and in all claims dependent therefrom. Applicant therefore requests withdrawal of the rejection under 102(b).

***35 U.S.C. § 103(a) Rejections: Peled et al. (WO 99/40783) in view of Lipton et al (US Patent Publication No: 2002/0090603), Wager et al (US Patent Publication No:2002/0001826, now US Patent No: 6,541,249) and Itskovitz-Eldor (US Patent No: 7,247,477)***

The Examiner has rejected claims 1 and 6 under 35 U.S.C. § 103(a), as allegedly being obvious over Peled et al (WO 99/40783) in view of Lipton et al. Claims 1 and 16 have been rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Peled et al. in view of Wager et al. Claims 1 and 19-22 have been rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Peled et al. in view of Itskovitz-Eldor et al. The Examiner's rejections are respectfully traversed. Claim 1 has now been amended.

As detailed above, now amended claim 1, and claims dependent therefrom, read on methods of *ex-vivo* expanding stem and/or progenitor cells by culturing in a stirred flask or rotating wall bioreactor, under stromal-free conditions allowing proliferation yet inhibiting

differentiation of the hematopoietic stem and/or progenitor cells, wherein the conditions include the presence of early acting cytokines and copper chelators. The Examiner has noted that Peled et al. teach a method of expanding hematopoietic stem cells from peripheral blood, marrow and cord blood, and reducing capacity of cells in utilizing transition metals by culturing with copper chelators (eg TEPA), but fail to describe selection via CD133. Further, the Examiner states that Lipton et al. describe methods for enriching CD133 and CD34 positive hematopoietic cells, and concludes that the combination of Peled et al. in view of Lipton et al. constitutes evidence for a *prima facie* case of obviousness. Applicant disagrees.

Applicant submits that the Examiner fails to provide evidence for a *prima facie* case of obviousness. Peled et al. merely discloses *ex-vivo* expansion of hematopoietic stem cells using copper chelators, whereas Lipton et al. merely teaches enrichment of CD133+/CD34+ cells from hematopoietic cells. However, neither Peled et al. nor Lipton et al. teach, suggest or provide motivation for the *ex-vivo* expansion of stem and/or progenitor cells in a stirred flask or rotating wall bioreactor. Thus, Peled et al. and Lipton et al, alone or in combination, do not, and cannot render the claimed invention obvious. Applicant respectfully requests withdrawal of the 103(a) rejection of claims 1 and 6 on the basis of Peled et al. in view of Lipton et al.

The Examiner has rejected claims 1 and 16 as being obvious over Peled et al. in view of Wager et. al. Applicant disagrees. Claim 1 has now been amended. Claim 16 has been canceled, rendering moot the rejection thereof.

While acknowledging that Peled et al. fails to describe culture of hematopoietic cells in a stirred flask or rotating wall bioreactor, the Examiner has stated that Wager et al. teach a method for culturing hematopoietic cells in vessels "...including stirred flasks, stirred tank reactors...", thus asserting that the combination of the teachings of Peled et. al and Wager et. al. render *prima facie* obvious the culturing and expansion of hematopoietic stem cells in stirred flask bioreactors as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Yet further, a *prima facie* case of obviousness can be rebutted if the applicant...can show that the art in any material respect 'taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." *In re Haruna*, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001)

Applicant submits that the Examiner has failed to meet the burden of establishing a *prima facie* case of obviousness of the claimed invention over Peled et al. in combination with Wager et al., as required *supra*, and that Wager et al clearly "teaches away" from the method of the claimed invention.

For clarity, Applicants are describing the teachings of Peled et al. and Wager et al. individually, but are traversing the rejection with respect to the combination of these references, *infra*.

- Peled et al. teaches *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem cells by culturing hematopoietic cells in a stroma-free culture with nutrients, cytokines and copper chelators, and does not teach culturing stem and/or progenitor cells in a bioreactor.
- Wager et al teaches immortalized stromal cell lines secreting cytokines, which cell lines support growth and induction of hematopoiesis in hematopoietic cells grown in culture dishes.

Wager et al. disclose the immortalization of human bone marrow stromal cell by retroviral transduction, resulting in production of immortalized stromal cell lines secreting combinations of cytokines and capable of supporting growth of hematopoietic cells. Examples include the growth to confluence, in culture dishes, of immortalized stromal cells to provide a feeder layer for *ex-vivo* growth of hematopoietic cells (see Wager et al, Example 3). However, hematopoietic cells grown according to the methods of Wager et al. invariably differentiate into mature blood cell types (Example 3 is titled "Immortalized Stromal Cells Support Hematopoiesis"), and no means for inhibiting differentiation is provided. Yet further, Wager et al. emphasize and demonstrate the cellular differentiating capabilities of their stromal cell lines, stating that the conditioned medium from the immortalized stromal cells "can be substituted for PHA-LCM (lecithin phytohemagglutinin) in methylcellulose assays"(see Wager et al., column 19, 2$^{nd}$ paragraph). Needless to say, the confluent stromal cell layer described by Wager et al is incompatible with the methods of expanding and inhibiting differentiation of stem and/or progenitor cells as claimed in the present invention.

Thus, rather than motivating to combine the teachings of Peled et al. with the methods of culture using immortalized stromal cells, Wager et al. teach away from using their methods for *ex-vivo* expanding and inhibiting differentiation of stem and/or progenitor cells in culture. Indeed, in view of the reported stimulation of hematopoietic differentiation using claimed stromal cell lines, one of ordinary skill in the art would not expect to combine Peled et al. and Wager et al. to expand and inhibit differentiation of hematopoietic stem and/or progenitor cells with a reasonable expectation of success.

Thus, the combination of Peled et al and Wager et al. do not teach or suggest, explicitly or inherently, methods for *ex-vivo* expanding and, at the same time, inhibiting differentiation of stem and/or progenitor cells by stromal- and feeder layer-free culturing with cytokines and copper chelators in stirred flask or rotating wall bioreactors, as alleged by the Examiner. Applicant submits that the Examiner has failed to make a *prima facie* case for obviousness over Peled et al alone, or in combination with Wager et al.

The Examiner has further rejected claims 1 and 19-22 under 35 U.S.C. § 103(a), as allegedly being obvious over Peled et al. in view of Itskovitz-Eldor et al. Claim 1 has now been amended. The Examiner's rejections are respectfully traversed.

While noting that Peled et al. fail to teach culture of stem and/or progenitor cells on a porous scaffold, the Examiner states that Itskovitz-Eldor et al. teach culture of vasculogenic progenitors on semi-solid alginate, matrigel, hydrogel or other scaffolds for production of *in-vitro* engineered vascular structures, thus curing the deficiency in Peled et al. for culture of hematopoietic stem and/or progenitor cells on a porous scaffold. Applicant disagrees.

As detailed above, Peled et al. fails to describe culture of hematopoietic cells in a stirred flask or rotating wall bioreactor. Yet further, Peled et al. do not suggest or motivate to culturing hematopoietic stem cells on a three-dimensional scaffold. Itskovitz-Eldor et al. teaches the differentiation of embryonic stem cells to form vasculogenic progenitor cells, their isolation and culture on semi-solid medium, to produce three-dimensional vascular tissue. No mention is made of growth of stem and/or progenitor cells in bioreactors. Indeed, culture of the vasculogenic progenitors taught by Itskovitz-Eldor et al. in a dynamic bioreactor such as a spinner flask or rotating wall vessel is incompatible with the production of three-dimensional structures described by the authors.

Thus, the combination of Peled et al and Itskovitz-Eldor et al. do not teach or suggest, explicitly or inherently, methods for *ex-vivo* expanding and, at the same time, inhibiting differentiation of stem and/or progenitor cells by culturing with cytokines and copper chelators in stirred flask or rotating wall bioreactors, as alleged by the Examiner. Applicant

submits that the Examiner has failed to make a *prima facie* case for obviousness over Peled et al alone, or in combination with Itskovitz-Eldor et al.

As detailed above, the combination of Peled et al. with Lipton et al., Wager et al. or Itskovitz-Eldor et al. is improper, and the suggested combinations do not (and cannot) teach or suggest the claimed method of *ex vivo* expanding stem and/or progenitor cells by *ex-vivo* stromal- and feeder layer- free culturing cells in a bioreactor with conditions for cell proliferation and a copper chelator, thereby inhibiting differentiation while permitting expansion of the hematopoietic cell population. In addition, there are secondary considerations present here, including unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

**Secondary Considerations That Must Be Considered**

Applicants' claimed method for *ex-vivo* expanding stem and/or progenitor cells by stromal- and feeder later-free culture with cytokines and a copper chelator requires culture in a dynamic, stirred flask or rotating wall vessel bioreactor. The claimed methods show an unexpectedly superior expansion of the hematopoietic population in total, as well as an unexpectedly superior selective expansion of the stem and progenitor populations therein (which is critical for short-term and long-term engraftment effectiveness of the expanded population).

As the specification demonstrates, the present invention teaches that *ex-vivo* expansion of hematopoietic cells in a stromal-cell and feeder layer-free dynamic bioreactor with cytokines and a copper chelator resulted in proliferation and greatly increased expansion of all stem cells tested (see Figs. 3-5 of the instant specification). Surprisingly, scaled-up stem and progenitor cultures grown in volumes suitable for use with stirred flask and rotating wall vessel bioreactors proved to be of greater efficiency in expanding the population of hematopoietic CD133+ progenitors than comparable cultures grown in static culture bags (see Figs. 6-8 of the instant specification) for equal time periods. Specifically, while fold expansion of total hematopoietic stem cells grown in stirred flask and rotating wall vessel bioreactors was up to double that of cells grown in cell-culture bags (see Figs. 3-5 of the instant specification), the fold expansion of CD133+ and CD133+/CD34- cells (early hematopoietic progenitors) grown in stirred flask or rotating wall vessel bioreactors was consistently greater by 10 to 40% or more than the static-grown cultures, with the effect most pronounced using lower seeding densities (see Figs. 6-8 of the instant specification). The significance of these results will be appreciated, considering that previous methods for

growing stem and/or progenitor cells in bioreactors required the incorporation of means for maintaining a stromal cell or feeder layer (see, for example, US Patent Nos: 5,541,107 to Naughton, et al.; 6,440,734 to Pykett, et al. and 6,911,201 to Merchav et al), restricting the cultures to continuous flow type reactors having attachment surfaces for the stromal cells, and obviating the use of more efficient dynamic reactors such as stirred flask and rotating wall vessel reactors.

The combination of the primary reference Peled et al. with any of Lipton et al., Wager et al., or Itskovitz-Eldor et al. could not lead the ordinarily skilled artisan to the surprisingly efficient methods of stromal- and feeder-layer free *ex-vivo* expansion of hematopoietic cells with cytokines and a copper chelator in bioreactors provided by the claimed invention.

***Double Patenting: US Patent No: 7,169,605; US Patent No: 6,835,867; US Patent Application No: 10/418,639 and US Patent Application No: 10/767,064***

The Examiner has rejected claims 1, 2-5, 7-11, 14 and 23 on the grounds of obviousness-type double patenting as being unpatentable over claims 1-6 and 8-11 of commonly assigned US Patent No: 7,169,605. In compliance with 37 CFR 1.321 (c), and as suggested by the Examiner, a terminal disclaimer, drafted and signed as set forth in 37 CFR 1.130(b), is attached herewith, thus overcoming the rejection on the basis of obviousness-type double patenting. Applicant notes the Examiner's reference to US Patent Application No: 6,835,867, which is an unrelated patent lacking common assignees and having claims 1-7 only, and has assumed that the intended reference was to US Patent No: 7,169,605.

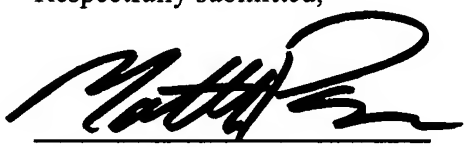
The Examiner has rejected claims 1, 2-5, 7-11 and 23 on the grounds of provisional obviousness-type double patenting as being unpatentable over claims 1-4, 8-15, 121, 123, 124, 126-128 and 131 of copending US Patent Application No: 10/418,639. In compliance with 37 CFR 1.321 (c), and as suggested by the Examiner, a terminal disclaimer, drafted and signed as set forth in 37 CFR 1.130(b), is attached herewith, thus overcoming the rejection on the basis of provisional obviousness-type double patenting.

The Examiner has rejected claims 1, 2-11 and 23 on the grounds of provisional obviousness-type double patenting as being unpatentable over claims 201, 209, 212, 213 and 238 of copending US Patent Application No: 10/767,064. In compliance with 37 CFR 1.321 (c), and as suggested by the Examiner, a terminal disclaimer, drafted and signed as set forth in 37 CFR 1.130(b), is attached herewith, thus overcoming the rejection on the basis of provisional obviousness-type double patenting.

## CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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